Wyeth

July 30, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Critical Path Initiative [Docket No. 2004N-0181, 69 Federal Register, 21839 – 21840, April 22, 2004]

Dear Madam/Sir:

Wyeth Pharmaceuticals is one of the world's largest research-based pharmaceutical and healthcare products companies and is a leading developer, manufacturer and marketer of prescription drugs, vaccines, biopharmaceuticals and over the counter medications. In the above-referenced Federal Register notice, FDA established a public docket to obtain input on activities that could reduce existing hurdles in drug development. The effort to identify such activities, or opportunities, is generally referred to as the "Critical Path" initiative. We are submitting the following comments to the public docket to provide Wyeth's recommendations concerning Critical Path opportunities.

Introductory Comments

In general, Wyeth supports the broad objectives of the Critical Path initiative - to identify opportunities to speed innovation, and to streamline the drug development process by making it more predictable, more efficient, and less costly. There are, however, several principles that must be kept in the forefront if this initiative is ultimately to be considered beneficial.

The first principle is that FDA must continue to adhere to all of its existing PDUFA commitments and goals. It is vitally important for FDA to maintain a continued focus on improving the efficiency and consistency of the regulatory review process even while new initiatives are undertaken toward improving the product development process. Second, as new, modern drug development tools become identified and applied, these new tools must replace and not add to the existing ones. Otherwise, efficiencies in drug development time and cost will not be realized, and collection of additional data could even add to the current regulatory burden. Third, given the Agency's current resource and budgetary

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constraints, it is conceivable that FDA may require additional resources in order to fully participate in the identification and evaluation of new drug development tools. This may require hiring additional staff, scientific training and devotion of staff time to Critical Path projects. If such proves to be the case, FDA should pursue the required additional funding through increased appropriations, not from PDUFA revenues.

In considering issues that represent significant drug development hurdles, the issues we have compiled fall into two broad categories. Some are scientific or methodological in nature, and others are recommendations for process improvements concerning FDA-sponsor interactions. In the scientific/methodological category we have cited the need for new endpoints and biomarkers (e.g., Alzheimer's Disease, cardiovascular disease) and new clinical trial methodology (adaptive design), and updating or clarification of regulatory standards (e.g., vaccine and antibiotic development). In the area of process initiatives we have identified the need for a better mechanism to involve senior FDA management personnel in meetings with sponsors regarding the use of innovative trial designs or novel endpoints, and the need for improved processes for expediting the phase 2 to 3 transition and for negotiating post-approval commitments. We believe these are significant opportunities for initiatives that could have a positive impact on the development of innovative new products and speed their availability to the patients who need them. Our specific Critical Path recommendations are discussed in greater detail below.

1. **Novel Approaches to Clinical Trial Design and Analysis**

   a) **Adaptive Clinical Trial Design** – the traditional approach to clinical development involves conducting modest-sized dose ranging studies in phase 2, followed by a larger confirmatory phase 3 study (or studies) once the results of the phase 2 trials have been analyzed. An "adaptive" clinical trial strategy would allow for midcourse adjustments to ongoing trials without stopping. The adaptive design would use the results of interim analyses to "fine tune" dose selection, treatment duration, sample size, and potentially other key parameters while allowing the study to continue. One major advantage of this approach is the elimination of "down time" between trials. Allowing investigators to continue to accrue

patients would maintain the momentum they had established in phase 2 through phase 3.

Another advantage of these adaptive strategies is that the number of patients who receive ineffective or possibly unsafe doses of the study drug would be reduced. Currently with fixed sample size trials, patients are enrolled to all treatment groups with out regard to emerging efficacy information obtained during the trial. An adaptive strategy could be designed to gradually favor higher performing treatments. Ethically it is preferable to reduce the patient exposure to doses that have limited efficacy or potentially important safety signals.

In order to implement adaptive strategies, an IT infrastructure must exist to permit rapid data acquisition, clean up, analysis, decision-making, and implementation. Use of standard data models such as CDISC would be highly recommended. It would also be useful to have standardized software and decision analysis tools to permit the rapid review and implementation of these approaches.

These approaches will require decisions for issues in three main areas. They are: 1) statistical methodology/experimental design issues, 2) technology/infrastructure issues, 3) regulatory process issues. A critical process question is who should have access to unblinded interim data. In many cases, sponsor personnel familiar with the project could most efficiently make midcourse study adjustments. Sponsors are often hesitant to perform an internal unblinded review because of concern that it could lead to bias and jeopardize the regulatory value of a study. A discussion of the scientific justification for this concern, along with guidelines for interim data review, would be of great interest. Another important process issue pertains to the sponsor-FDA interactions. If FDA, for example, wanted to participate in the decision on which treatment arms should continue in the trial, establishing a mechanism for prompt communication would be essential for minimizing any disruption of the study.

Once these issues have been resolved, adaptive design strategies could improve efficiency, require smaller treatment groups, and generally reduce the time and cost of clinical development. Wyeth recommends that FDA

work with industry to pilot the adaptive design concept, evaluate its benefits, and develop draft guidance if the potential benefits and feasibility are demonstrated.

b) **Mechanism for Senior-Level FDA input** – the current regulatory review process does not have a clear mechanism for involving the most senior and experienced FDA management personnel in discussions with sponsors regarding novel clinical trial design or endpoints. While senior FDA management will often encourage the exploration of novel approaches, when such designs are presented and discussed with review staff there is often a tendency to gravitate back to the older, previously tried approaches. Since the most senior-level (e.g., Office Director, Center Director) CDER and CBER management personnel are not routinely available to attend Agency-sponsor meetings on clinical protocol design, their experience and perspective (and acceptance of innovation) may not be reflected in the advice that the sponsor hears when meeting with the Agency. A sponsor may appeal a decision or request a followup meeting, but precious time may be lost resulting in a delay of the clinical trial while waiting for FDA's response or another meeting. An additional drawback is that sponsors may be reluctant to appeal a decision due to concerns that doing so will harm the working relationship with the reviewing division.

   Wyeth, therefore, recommends that FDA develop a process to enable a sponsor to obtain the input of the Agency's most experienced and senior review management personnel on issues pertaining to novel design of clinical trials or novel endpoints. This would benefit drug development by facilitating the application of modern science to the clinical trial process. It would also benefit Agency review personnel at the primary review level by engaging the most senior, experienced personnel in trial design issues involving cutting-edge science.

c) **Co-Primary Endpoints** – traditional statistical approaches are available to deal with the situation of multiple co-primary endpoints where efficacy can be demonstrated through achieving statistical significance on one or more of the endpoints. Another type of multiplicity problem (often referred to as "reverse multiplicity") is arising more frequently, where efficacy can be demonstrated only through achieving statistical

significance on all of the co-primary endpoints. A similar problem occurs with combination therapy, where the combination must be shown to be superior to each component, or when multiple analyses are required to show significance (e.g., an ITT and a per protocol analysis, or two approaches for dealing with missing data). The implications of reverse multiplicity on Type I and Type II error should be fully explored. Opportunities to avoid the problem by identifying a primary analysis within a hierarchy should be investigated, both in general and within specific disease areas. When co-primary endpoints are considered necessary to characterize all dimensions of the clinical situation, alternative statistical methods should be examined to control Type I error without unnecessary loss of power. In particular, it should not be considered essential to achieve statistically significant results at the traditional $p<.05$ level for each co-primary endpoint for the trial outcome to be deemed successful.

2. **New Endpoints for Alzheimer's Disease**

There is a desperate need for additional safe and effective therapies for treating Alzheimer's Disease. There is also a corresponding need for greater regulatory receptivity to utilization of new clinical trial endpoints for demonstrating effectiveness. The current accepted standard, the Alzheimer's Disease Assessment Scale for cognition (ADAS-Cog) evolved during the development and approval of the initial class of products approved for treating the symptoms of Alzheimer's, the cholinesterase inhibitors. However, there are promising new and innovative treatment alternatives presently under investigation that are thought to work by completely different mechanisms than the currently approved therapies (cholinesterase inhibitors and memantine). In addition, many of these new therapies are targeted toward disease modification, an effect which may be qualitatively different from that of the currently approved therapies, which target only the symptoms of the disease The ADAS-Cog may not be the only, or the most appropriate tool for assessing the effectiveness of these emerging investigational therapies. Alternate cognitive measures may be more appropriate for measuring the effect of disease modifying agents and these are under active investigation. In addition, surrogate markers of disease progression, such as quantitative MRI measures, measurements of glucose metabolism and amyloid content by PET scanning, and CSF or other biomarkers may also be useful in demonstrating the effect of potential disease modifying therapies. The FDA should be willing to consider the use of these alternate endpoints in the evaluation of the

effectiveness of disease modifying agents, and be open to a dialogue as to which endpoints might be used to gain accelerated approval for these compounds through existing mechanisms. With this flexibility, it may be possible to speed the eventual approval of therapies targeted toward slowing the progression of this devastating disease.

3. **New Biomarkers and Surrogate Markers for Cardiovascular Diseases**
Early cardiovascular disease detection / risk stratification supports an aggressive preventive strategy, and thus, is a critical clinical objective of all new drug development programs. In evaluating the utility of non-mortality cardiovascular surrogates, IVUS, CIMT, and markers of inflammation are currently lead candidates that could be used in this manner. Longitudinal studies to establish the correlation of these surrogates to reductions in cardiovascular events such as stroke, myocardial infarction and cardiovascular death are needed before implementation and acceptance of these surrogates can be undertaken. Nevertheless, as emerging new therapies have prevention as the ultimate goal, the importance of these surrogates will undoubtedly increase over time. Therefore, these emerging cardiovascular markers and imaging techniques provide an opportunity for early disease detection and risk stratification, and this is becoming a critical clinical objective as novel preventive therapies become available providing opportunities for earlier intervention. Two of the nearer term possibilities for use of biomarkers in the cardiovascular disease area are discussed in greater detail below.

   a) **Intravascular Ultrasound (IVUS)** - Coronary intravascular ultrasound (IVUS) technology is an innovative approach for the evaluation of coronary vascular pathology, and for the guidance of interventional procedures. This technique affords the ability to measure not only lumen size, but also detailed descriptive information regarding plaque composition and plaque morphology. IVUS measurements provide 3-dimensional data, with accurate quantification of plaque volume, and do not require administration of radiographic contrast agents. These properties provide significant advantages over traditional coronary angiography. Traditional coronary angiography lacks the sensitivity of IVUS to detect early lesions and lesions with extensive atherosclerotic vascular remodeling, and may fail to detect disease in younger individuals who are less likely to have extensive atherosclerosis.

Recent data from two companion trials, comparing two different lipid-lowering regimens, suggest a correlation between inhibition of progression of atherosclerotic plaque on IVUS, and long-term clinical event reduction. REVERSAL, which used IVUS to quantify atherosclerotic plaque burden in a population with chronic coronary heart disease (Nissen, et al., 2004), and PROVE-IT, which assessed incidence of major cardiovascular events following acute coronary syndromes (Cannon, et al., 2004), concurred in their demonstration of the superiority of atorvastatin 80 mg over pravastatin 40 mg. Correlations between effects on lesion progression and reductions in major vascular events in large, well-controlled trials are intriguing. However, these observation datasets will need to be prospectively confirmed.

Assessments of atheroma burden have been used to assess cardiovascular risk, and IVUS has been used to provide preliminary assessment of efficacy of novel preventive therapies in early drug development (Nissen, et al., 2003; Tardif, et al., 2003). Quantitative coronary angiography (QCA) and carotid intima-media thickness (CIMT) have regulatory precedent to serve as the basis for approval of efficacy claims for atherosclerosis modulation. Primary among these have been the claims associated with HMG-CoA reductase inhibitors. IVUS endpoints have been used in support of applications for approval for intracoronary devices. With its superior sensitivity when compared to QCA, and excellent reproducibility, IVUS should be an acceptable endpoint to defend efficacy claims regarding modulation of atheroma burden, such as claims of slowing of progression of coronary atherosclerosis. In addition, the potential for IVUS measurements to serve as confirmatory evidence of efficacy for novel cardiovascular preventive therapies should be further evaluated.

New information suggests, however, that plaque volume quantification may not be sufficient to provide comprehensive risk evaluation as it relates to secondary and/or primary cardiovascular risk reductions for MI, stroke, and cardiovascular death. It has long been recognized that acute coronary events frequently arise from thrombosis in sites with minimal luminal stenosis, suggesting that other properties of atherosclerotic lesions contribute significantly to risk of acute destabilization. Histopathologic data have provided convincing evidence that morphologic features such as lipid content, fibrous cap thickness, and inflammatory cell content correlate with acute cardiovascular events, whereas degree of stenosis is only weakly correlated with plaque disruption (Falk, et al., 1995). Plaque morphology, characterized by IVUS, has been correlated with subsequent

acute events (Yamagishi, et al., 2000). The ability of IVUS to provide information about plaque morphology and composition may allow this technique to be used to assess plaque vulnerability; however, the longitudinal data that would confirm the relationship between changes in plaque composition by IVUS and subsequent reduction in acute plaque rupture and/or acute coronary events is still lacking and must be developed.

b) C-Reactive Protein (CRP) – A large body of scientific and clinical data, including data from numerous large, prospective clinical trials, supports the importance of inflammation as a key driver in the pathophysiology of atherosclerotic vascular disease. Markers of inflammation, therefore, may serve as valuable predictors of cardiovascular risk, as well as potential surrogate endpoints in cardiovascular interventional trials.

C-reactive protein (CRP), measured using a high-sensitivity assay, has been epidemiologically correlated with long- and short-term cardiovascular outcomes as a risk factor, in both primary and secondary prevention populations. Individuals with high-risk CRP levels (e.g., levels > 3.0 mg/dL) have an approximate 2-fold increase in risk of future cardiovascular events. By comparison, a 30 mg/dL increase in LDL-C confers a 30% relative increase in risk. Confirmation of the independent value of CRP levels, for prediction of likelihood of future major cardiovascular events, has led to the publication of clinical guidelines recommending the use of this marker (Pearson, et al., 2003). The low variability and longitudinal stability of CRP levels, and the ready availability of reliable, validated commercial assays for high-sensitivity CRP (hs-CRP), make CRP the inflammatory marker of choice for clinical use. CRP levels correlate well with incidence of major clinical events, but not well with global measures of extent of atherosclerotic lesion, suggesting that the measurement of CRP may provide insight into lesion vulnerability, a quantity that has not been well-characterized using radiographic techniques (Ridker, et al., 2004). Although an independent link between CRP-lowering and risk reduction has not been verified, large interventional trials have demonstrated that therapies that reduce cardiovascular risk also lower CRP and other markers of inflammation (literature on HMG-CoA reductase inhibition recently reviewed in Balk, et al., 2003), and that patients with elevated CRP may derive greatest clinical benefit from aggressive treatment (Ridker, et al., 1997; Ridker, et al., 2001; Lindmark, et al., 2001).

Accordingly, there is tremendous potential utility of this biomarker in cardiovascular drug development. Elevated CRP can clearly serve as a biomarker of cardiovascular disease risk, and potentially guide patient selection for specific anti-inflammatory or other preventive therapy (Ridker, et al., 2003). Presence of an early CRP response could potentially identify patients more likely to benefit from long-term therapy. Reduction of CRP may serve as a supportive indicator of drug mechanism and likelihood of therapeutic risk reduction. Magnitude of CRP reduction could, in the setting of mechanistically appropriate interventions, provide guidance for dose-selection or intensification of therapy. Many of these relationships require verification through future research efforts. Support of such effort could provide an opportunity to maximize the impact of new scientific understanding of the pathophysiology of atherosclerotic disease on the development of novel, targeted therapies for the reduction of cardiovascular risk.

4. **Development of New Antibiotics**

The emergence in recent years of resistant strains of pathogens has continued to reinforce the medical need for development of innovative new antibiotic treatments. However, one significant hurdle and disincentive for development of new antibiotics is the statistical criteria that FDA has adopted in its guidance for clinical studies of antibiotics. Until recently, a 15% delta was considered acceptable. Now, in basic terms, these criteria require that the difference (delta) in response rates between two treatments that are compared in a study designed to show non-inferiority must not exceed 10% in order to conclude that the two treatments were not different from one another. The impact of applying the more rigorous standard is that antibiotic trials must now be designed with larger sample sizes to minimize the probability of a result due to chance that exceeds the 10% delta. To illustrate the impact, if 80% cure rates are assumed for both the test drug and active control with 90% power, and the determination of non-inferiority based on a two-sided 95% confidence interval:

Delta = 15% requires 150 patients per treatment group
Delta = 10% requires 337 patients per treatment group

As seen in this example, the more rigorous delta more than doubles the number of patients required for the study, with commensurate increases in the time and cost for completing the study. Furthermore, the focus of a non-

inferiority analysis is on the "evaluable" patient population and for certain types of infections the non-evaluability rate can be quite high. Considering the serious public health consequences associated with the emergence of resistant microorganisms and the dearth of new antibiotics that are being introduced to the market to combat these threats, the FDA should reconsider its current guidance concerning the delta issue. The Agency should evaluate if requiring the 10% delta is truly in the best interest of public health or whether a 15% delta would be scientifically acceptable and more likely to promote the development of innovative new antibiotics.

Another area of opportunity for antibiotic development is the approach currently used by FDA for review and approval of the clinical laboratory susceptibility tests. Under the current process, the application for a susceptibility test kit is only reviewed and approved after FDA has already approved the new drug application for a new antibiotic. Since these test kits are essential for proper use of the antibiotic by infectious disease specialists, this sequential approach delays the market introduction and use of the new antibiotic. It is recommended that FDA evaluate whether review of the susceptibility test kits could be done in parallel with review of the antibiotic new drug application, potentially expediting availability of new antibiotics by eliminating the lag between approval of the new antibiotic and availability of the test kit.

5. **Development Issues for Vaccines**

There are a number of Critical Path issues impacting the development of new vaccines. The clinical development programs for new vaccines typically involve evaluation of much larger numbers of subjects than are typically studied for most new drug products. Consequently, the overall time for development and product introduction tends to be longer. There is a need for greater clarity on the expectations for numbers of subjects to be studied, the rationale for determining the size of the safety database, and how many subjects must be studied in the pre-approval phase versus post-approval surveillance.

Another aspect of vaccine development that is a substantial hurdle is the requirement to conduct compatibility/interference studies with other vaccines commonly administered according to the routine childhood vaccination schedule. The number of comparisons that are required is likely to lead to statistical failures, simply due to chance. It is recommended that FDA

develop guidance to address, among other things, standardization of the statistical comparisons for compatibility studies (e.g., to eliminate the co-primary outcomes for both GMTs and % responder, and rely only on the latter), publication of accepted values for each antigen to use as the responder level based on standardized assays, and definition of the antigens to be compared for each licensed vaccine. A risk-benefit approach is needed that is not excessive concerning the number of studies and sample sizes.

6. **Regulatory Consistency**

Having transparent and consistent regulatory standards would benefit the development of innovative therapies by reducing one source of the unpredictability that is inherent in the drug development process. Special requirements are sometimes justifiable based on unique class effects or due to unique risk-benefit considerations for a category of products. However, aside from such special circumstances FDA should ensure there is a high level of consistency across review divisions, Offices and Centers concerning the overall requirements for demonstrating safety and effectiveness, size of the database, numbers of patients required for long-term safety, etc. Some areas where there have been differences observed in review division practices include criteria for allowing patient enrollment in long-term treatment extensions, criteria for enrollment of women of childbearing potential, and requests for submission and review of data from one phase of a study (e.g., dose level) before allowing the next phase of the study to proceed. Wyeth recommends that FDA perform an evaluation to ensure consistency across review divisions, identify where there are differences in the standards required for approval of new products, and ensure that consistent standards are applied unless clear justification for such differences can be identified.

7. **Phase 2 to Phase 3 Transition**

FDA encourages sponsors to request an end-of-phase 2 meeting to discuss results obtained from phase 1 and phase 2 development, the phase 3 development plan and the design of the major phase 3 protocols. Such meetings are extremely valuable and should continue to be held on a routine basis. However, significant critical path time can be lost between the completion of phase 2 and the initiation of phase 3 studies. One contributing factor is the expectation that sponsors will provide a meeting background document summarizing the phase 2 results. This requires time to process and

evaluate data, prepare and submit a summary to FDA, and a waiting period of at least 4 weeks for a meeting date. Because the EoP2 discussion may influence decisions about the phase 3 development plan, additional time may be lost while the sponsors revise and submit the phase 3 protocols to FDA before the studies can be initiated.

The transition from phase 2 to 3 could be made more efficient if the gap can be narrowed between completion of the phase 2 studies and submission of the finalized phase 3 protocols. One approach toward this goal would be to utilize data tables in the EoP2 meeting background document that would be generated as soon as possible after data is collected from the last patient visit, without pausing to write up detailed narrative summaries interpreting the data. The interpretation would be discussed and explained, as necessary, at the EoP2 meeting. The FDA would have to be willing to accept EoP2 background documents that would include more tabulation of data rather than narrative summaries, and if the actual scheduling of the meeting is also accelerated the gap between phase 2 and initiation of phase 3 could be substantially reduced.

8. **International Harmonization**

During the past decade substantial progress has been made toward harmonizing scientific and regulatory standards among the regions of the world participating in the ICH process. Despite such efforts, however, major differences remain that contribute to prolonging the time and cost of developing innovative new therapies. Consequently, additional studies, or expanded studies with additional treatment arms are often performed to satisfy the different regulatory/legal requirements of the United States, European Union, and Japan. Many opportunities still exist to improve the efficiency of the drug development process through further harmonization of scientific and regulatory requirements with other regions of the world. In addition, harmonization will be extremely important once new tools for assessing safety, effectiveness and manufacturing are identified and implemented. Most of the companies that are responsible for developing and bringing innovative new therapies to patients are multi-national firms with a global approach to their drug development programs.

In the grand scheme of global development, adoption of new tools for demonstrating safety and effectiveness for the US may not reduce overall time and cost for drug development unless the implementation of new tools is coordinated internationally through the harmonization process. In fact, there is some risk that it could actually increase development costs if new approaches are adopted for the US while traditional methodology is still required for Europe, Japan and elsewhere around the world. For these reasons, Wyeth recommends that once the Critical Path opportunities list has been identified, FDA should seek international participation on key Critical Path opportunities to maximize the potential for global acceptance, particularly with respect to new study designs, clinical trial endpoints and statistical methodologies.

9. **Post-Marketing Commitments**

There is a clear need for significant improvement in the process for how post-marketing commitments are requested of sponsors. In fact, there does not presently appear to be any standard process for how this is handled across FDA review divisions and Centers. Requests for post-approval commitments are often communicated to the sponsor very late in the review process, sometimes immediately prior to the user fee action date. In many cases there is insufficient time for a reasonable dialogue to occur between the review division and the sponsor regarding the merits and feasibility of the request. Sponsors may even feel pressured to agree to such requests in order to avoid jeopardizing the pending approval of their application. It might be argued that the process for negotiation of post-approval studies is not a drug development issue, and hence not on the Critical Path. However, the resources required to fulfill post-approval commitments (especially clinical studies) are significant. Since industry resources for discovery and development are finite and the costs of drug development have been steadily rising, any R&D funds that are used for fulfilling post-approval commitments generally translates to less funding for innovation and development of new therapies. Hence, the utilization of R&D resources for post-approval commitments has a direct bearing on resources available for innovation and drug development.

There are undoubtedly many situations where post-approval commitments are necessary and appropriate. This is generally the case when a product is approved under the subpart H, accelerated approval regulation, when additional studies are needed to confirm clinical benefit. There are other situations when post-approval studies are needed to answer genuine questions

regarding the safety or effectiveness of the product that were not addressed during the premarketing development program. The fact that there are situations when requests for important post-approval commitments are appropriate only underscores the need for having a clear and robust process for how they are vetted and agreed upon. Otherwise the sponsor may feel forced to agree to a study that is not feasible to perform, or that may not answer the outstanding issues regarding the safe and effective use of the product within a reasonable time frame.

Wyeth therefore recommends that FDA develop a guidance for reviewers to delineate a clear process for requesting post-approval commitments. The guidance should address the following areas:

a) Criteria for identification of the questions of safety or effectiveness that need to be addressed (avoiding requests for "nice-to-know" scientific questions), and the level of FDA management to be consulted regarding the appropriateness of the request before it is communicated to the sponsor.
b) Timing for communicating such requests to the sponsor, and in particular, allowing a reasonable period of time for Agency-sponsor dialogue prior to the user fee action date.
c) Mechanism for FDA senior management involvement in the final negotiations with the sponsor.

10. <u>Drug-Device Combination Products</u>

The agency's critical path initiative addresses the use of new technologies to facilitate the development of novel products. Increasingly these novel products will be drug or biological/device combination products. Although the agency's review procedures for these products have improved significantly over the last few years, additional improvements are needed to facilitate the timely development of these products. The following measures are suggested:

a) One of the most promising aspects of the agency's Critical Path Initiative is that it focuses on making all phases of development more efficient rather than only the relatively shorter approval process. With regard to combination products, there remains too little input from non-lead review Centers during the early stages of combination product development programs. This has led to significant

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development delays due to new and unpredicted requirements entering the critical path too late in development to implement efficient solutions. The routine use of intercenter review teams would help to avoid such problems.

b) Too often, drug/device combination products that are reviewed under the drug approval procedures have traditional drug, rather than device, development paradigms applied. For example, three phases of clinical development are often required for drugs rather than the more flexible "pilot" and "pivotal" phases typical during the clinical development of devices. For certain drug/device combinations, the use of device development paradigms may lead to more efficient development programs.

c) Although there are efforts already underway, we wish to underscore the need for additional reviewer training on combination product review procedures. Too often reviewers from non-lead centers are unclear on their role, and reviewers from lead centers are unfamiliar with how to efficiently incorporate input from non-lead Centers into the review process. Continued emphasis on training is needed to improve the coordination and interactions between the respective review personnel.

Wyeth appreciates having the opportunity to comment on the FDA's Critical Path initiative, and we trust that the recommendations and ideas that we have provided will be helpful to the Agency's efforts to prioritize the Critical Path opportunities list.

Sincerely,

Roy J. Baranello, Jr.

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Worldwide Regulatory Affairs

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Bibliography: Intravascular Ultrasound (IVUS)

Cannon, CP, et al. Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes. PROVE IT – TIMI 22 Investigators. *NEJM* (2004) 350.

Falk, E, et al. Coronary plaque disruption. *Circulation* (1995) 92:657-71.

Fayad, ZA, et al. Clinical imaging of the high-risk or vulnerable atherosclerotic plaque. *Circ Res* (2001) 89:305-316.

Newby, DE, et al. Invasive assessment of the coronary circulation: intravascular ultrasound and Doppler. *Br J Clin Pharmacol* (2001) 53:561-575.

Nissen, SE, et al. Effect of recombinant ApoA-1 Milano on coronary atherosclerosis in patients with acute coronary syndromes. *JAMA* (2003) 290:2292-2300.

Nissen, SE, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis. REVERSAL Investigators. *JAMA* (2004) 291:1071-1080.

Sosnovik, DE, et al. Noninvasive imaging of plaque vulnerability: an important tool for the assessment of agents to stabilise atherosclerotic plaques. *Expert Opin Investig Drugs* (2002) 11:693-704.

Tardif, J-C, et al. Effects of AGI-1067 and probucol after percutanous coronary interventions. *Circulation* (2003) 107:552-558.

Taylor AJ, et al. 34th Bethesda Conference: "Can atherosclerosis imaging techniques improve the detection of patients at risk for ischemic heart disease?" *J Am Coll Cardiol* (2003) 41:1855-1917.

Yamagishi, M, et al. Morphology of vulnerable coronary plaque: insights from follow-up of patient examined by intravascular ultrasound before an acute coronary syndrome. *J Am Coll Cardiol* (2000) 35:106-111.

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Bibliography: C-Reactive Protein (CRP)

Balk, EM, et al. Effects of statins on nonlipid serum markers associated with cardiovascular disease. *Ann Intern Med* (2003) 139:670-682.

Ballantyne, CM, et al. Lipoprotein-associated phospholipase A1, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* (2004) 109:837-842.

Danenberg, HD, et al. Increased thrombosis after arterial injury in human C-reactive protein-transgenic mice. *Circulation* (2003) 108:512-515.

Danesh, J, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ (2000) 321:199-204.

Danesh, J, et al. C-reactive protein and other circulatory markers of inflammation in the prediction of coronary heart disease. *NEJM* (2004) 1387-1397.

Lindahl, B, et al. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. *NEJM* (2000) 343:1139-1147.

Lindmark, E, et al. Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy. *JAMA* (2001) 286:2107-2113.

Pearson, TA, et al. AHA/CDC Scientific Statement: Markers of Inflammation and Cardiovascular Disease, Application to Clinical and Public Health Practice, A Statement for Healthcare Professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* (2003) 107:499-511.

Ridker, PM, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *NEJM* (1997) 336:973-979.

Ridker, PM, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *NEJM* (2000) 342:836-843.

Ridker, PM, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. Air Force / Texas Coronary Atherosclerosis Prevention Study Investigators. *NEJM* (2001) 344:1959-1965.

Ridker, PM, et al. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. JUPITER Study Group. *Circulation* (2003) 108:2292-2297.

Ridker, PM, et al. Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. *Circulation* (2004) 109(Suppl. IV):IV-6-IV-19.

Ross, R. Atherosclerosis: an inflammatory disease. *NEJM* (1999) 340:115-126.